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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,041	02/14/2002	Hideki Ishihara	0397-0440P	6640

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,041	ISHIHARA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-9* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/14/02, ~~6/26/02~~ ~~10/2/03~~ 9/30/03 (2/14/02)
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/15/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Ishihara et al.

1. Claims 1-9 are pending. Claim 6 as it is drawn to CDK 2 and claims7-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention for the reasons set forth below. Claims 1-6 as they are specifically drawn to CDK1 are currently under prosecution.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7, drawn to a method for determining the activity of a cell cycle regulatory factor, classified in class 435, subclass 4.

II. Claims 8 and 9, drawn to a method of diagnosing cancer, classified in class 424, subclass 9.1.

3. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I and II represent groups that encompass different objectives, method steps and populations which would present different response variables, and criteria for success. In the instant case, different searches would be required for examining methods of diagnosing

cancer in human patients versus examining methods of measuring cyclin-dependent kinase activity in cells.

4. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

Species Election:

Claim 1 is generic to a plurality of disclosed patentably distinct species comprising the following: CDK1, CDK2, CDK4, and CDK6, claim 2.

The products of the above species represent separate and distinct molecules with different structures and functions that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

5. During a telephone conversation with Mr. Weiner on April 15, 2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-7 and a species selection of CDK1 in claim 2. Because applicant did not distinctly and

specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1-6 are rejected as being vague and indefinite because claim 1 does not contain a positive process step which clearly relates back to the preamble.

7. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, because claim 1 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is: a wash step to remove excess label from the product needed to reduce high background during measurements.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the activity of a cyclin-dependent kinase (CDK), does not reasonably provide enablement for a method for determining the activity of a cell cycle regulatory factor comprising the claimed steps. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-6 are drawn to a method of determining the activity of a cell cycle regulatory factor. This means the claims are drawn to determining the activity of any cell cycle regulatory factor. The specification teaches that there mainly exist two groups of cell cycle regulatory factors in cells. One is a group of kinases which are positive regulatory factors and are referred to as cyclin-dependent kinases (CDKs), and the other is a group of CDK inhibitors (CDKIs) which are negative regulatory factors. The CDKs exist in cytoplasm as inactive form. The CDKs are activated, e.g., phosphorylated, and move into nuclei in the cells. In the nuclei, the CDKs bind to cyclin molecules to form complexes with cyclin (referred to as activated CDKs hereinafter) and positively regulate the

progress of the cell cycle at various steps of the cell cycle. On the other hand, the CDKIs inactivate the CDKs by binding to the activated CDKs, thereby regulating the cell cycle negatively (page 3, lines 1-13). The specification teaches how to determine the activity of CDKs (Examples 1-4). The specification further teaches how to determine the specificity of CDK activity with the use of CDK inhibitors (Example 6).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification clearly teaches that there mainly exist two groups of cell cycle regulatory factors in cells. Given this teaching it appears that there are more, undefined groups of cell cycle regulatory factors in cells. However, the specification teaches only the CDKs and the CDKIs. Given the undefined nature of the broadly claimed group it is clear that one would not be able to assay the activity of these undefined cell cycle regulatory factors based only on the information in the specification and the art of record, in particular, if they are not kinases. Further, as drawn to the CDKIs, although the specification clearly teaches how to use CDKIs to determine the specificity of CDKs, the specification is not drawn to any assay specific for the determination of the activity of CDKIs and the claims as currently constituted do not teach an assay that one of ordinary skill would expect to be able to use to determine the activity of any CDKI with a reasonable expectation of success.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict

that the claimed invention of determining the activity of a cell cycle regulatory factor would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Note: If applicant were to overcome the preceding scope of enablement rejection, the following claims would still be rejected under 35 U.S.C. 112, first paragraph, scope of enablement:

9. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining activity of a cell cycle regulatory protein comprising an assay of a substrate that does not naturally contain thiol groups or said substrate where natural thiol groups are blocked, it does not reasonably provide enablement for assaying any substrate and does not account for the error of increased fluorescence from labeling these naturally occurring thiol groups on the substrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-6 are drawn to a method of determining the activity of a cell cycle regulatory factor comprising introducing a monothiophosphate group onto the substrate, labeling the substrate by coupling a labeling fluorphore or a labeling enzyme with a sulfur atom of the introduced monothiophosphate group, and measuring the amount of

fluorescence from the labeling fluorophore labeling the substrate, or reacting the labeling enzyme labeling the substrate with a substance which generates an optically detectable product by reaction with the labeling enzyme and optically measuring the amount of the generated product. This means that the claims are drawn to a method of determining the activity of a cell cycle regulatory factor comprising a step of using any substrate for the CDK, including those that naturally contain a thiol group. The specification teaches that the cysteine residue in substrates, such as Rb, is substituted by an amino acid residue such as alanine which does not contain a thiol group. This is for avoiding measurement errors owing to the labeling of the thiol group of the cysteine residue essentially present in the substrate when assaying for the substrate containing the introduced thiophosphate group. The specification teaches that regarding a substrate wherein essentially contains the cysteine residue in its molecules, it may be possible to produce, from the substrate, a substrate of which the cysteine residue is substituted by an amino acid residue such as alanine which does not contain the thiol residue, by PCR or by modifying a gene of the substrate by site mutagenesis and expressing the modified gene (pages 14 and 15).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification teaches that substrates naturally containing cysteine residues, hence a thiol group, may contribute to measurement errors when determining the activity of a cell cycle regulatory factor. It is noted that the art recognizes the difficulties associated with background fluorescence when assaying fluorescently labeled substrate in a mixture of substrate that contains thiol groups that are additionally

labeled. In agreement with the specification, the effects of background sensitivity of fluorescence assays are well known, for example, US Patent No. 4,529,313 specifically teaches that immunoassay is a field where sensitivity is of prime importance due to the low analyte levels that are measured. The sensitivity of fluorescence assays, although theoretically very high, is limited by the presence of background fluorescence. In many situations it is impossible to reduce the background sufficiently (by filtration and other techniques known in the art) to obtain the desired sensitivity. US Patent No. 4,252,783 teaches that one of the problems with fluorescence is the number of factors which contribute to background values. Included among these factors are light scatter, instrument variation, fluorescent reagent contamination, and endogenous fluorescence in the sample. Given the above, it is clear that the effects of background sensitivity in fluorescence assays can lead to measurement errors and inaccurate results which makes it difficult or impossible to determine the effects of adding a thiol group to any substrate and distinguishing between background substrate and labeled product as described above. The claims as currently constituted do not teach an assay that one of ordinary skill would expect to be able to use to determine the activity of a cell cycle regulatory factor using any substrate for a CDK with a reasonable expectation of success. Further, it would be expected that similar problems with assay sensitivity would be found with any substrate for enzyme assay.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict

that the claimed invention of determining the activity of a cell cycle regulatory factor by using any substrate for the CDK would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 1, 2, 3, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (*J Biol Chem*, 1993, Vol. 268: 20443-20451) in view of Jeong and Nikiforv (*BioTechniques*, 1999, Vol. 27: 1232-1238, IDS) and Facemyer and Cremo (*Bioconjug Chem*, 1992, Vol 3: 408-413, IDS).

Claims 1, 2, 3, and 6 are drawn to a method of determining the activity of a cell cycle regulatory factor comprising reacting ATP-γS with a substrate for a CDK, labeling the substrate with a fluorophore, measuring the fluorescence from the label in the product, calculating the activity of the CDK from the measured amount of label in the product with reference to a pre-produced curve (claim 1), CDK1 (claim 2), fluorescent dye (claim 3), and a histone H1 substrate (claim 6).

Pan et al. teach a method for determining the activity of cdc2 (CDK1) comprising incubating a CDK1/cyclin complex with [γ-^{32}]ATP and histone H1 and measuring CDK1

phosphorylation activity by quantifying [^{32}P] in the product and comparing it to control measurements (page 20444). Pan et al. does not teach reacting ATP-γS with a substrate, labeling the substrate with a fluorophore, and measuring the fluorescence from a labeled substrate.

Jeong and Nikiforv teach a non-radioactive method of detecting protein kinase activity comprising reacting ATP-γS with a substrate, kemptide (which does not naturally contain a thiol group), to create a thiophosphorylated product (page 1232, column 3) and measuring fluorescence values in the final product (page 1233, columns 1 and 2). The reference teaches that the biggest drawback of the present method is the relatively slow rate of the biotinylation step, however this can be overcome by various methods and thus it represents a viable alternative to existing methods of screening protein kinases (page 1238, column 2). The reference suggests this method is useful for a wide range of different kinases (page 1232, third column). Further, the reference teaches that presented is an alternative approach for detecting kinase activity wherein the method does not require the use of radioactivity and allows flexibility in the detection scheme (p.1238, column 2).

Facemyer and Cremo teach a method of using a protein kinase and ATP-γS to create a thiophosphorylated protein and the method of labeling a thiophosphorylated protein by coupling the sulfur of the protein phosphorothioate to a fluorescent haloacetate (page 409). It is noted that the reference further teaches that thiol groups in the substrate are blocked prior to reaction with ATP-γS (See Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the methods of Jeong and Nikiforv for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate because Jeong and Nikiforv specifically teach the disadvantages of traditional assays of enzyme activity of protein kinases which use [γ-^{32}]ATP which require radioactivity and multiple steps. One would have been motivated to substitute the methods of Jeong and Nikiforv for the method of Pan et al. to assay CDK1 activity with a histone H1 substrate in order to eliminate the disadvantages specifically taught by Jeong and Nikiforv and because Jeong and Nikiforv specifically suggest that the method is useful for a wide range of different kinases. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to substitute the direct fluorescent labeling of the thiol of the reacted ATP-γS of Facemyer and Cremo for the labeling steps of the combined references because Jeong and Nikiforv specifically teach that the biggest drawback of their method is the relatively slow rate of the biotinylation step. One would have been motivated to substitute the direct fluorescent labeling of the thiol of the reacted ATP-γS of the Facemyer and Cremo for the labeling steps of the combined references in order to save not only time, but also the cost of the labeling reagents of Jeong and Nikiforv.

11. Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al., Jeong and Nikiforv, and Facemyer and Cremo and in further view of Hemmila (*Clin. Chem.*, 1985, vol. 33, pages 359-370).

The claims are drawn to a method of determining the activity of a cell cycle regulatory factor comprising reacting ATP-γS with a substrate for a CDK, labeling the substrate with a fluorophore, measuring the fluorescence from the label in the product, calculating the activity of the CDK from the measured amount of label in the product with reference to a pre-produced curve (claim 1), and a fluorescent dye FITC (claim 4).

Pan et al., Jeong and Nikiforv, and Facemyer and Cremo teach as set forth above. However, the combined references do not specifically teach labeling the substrate with FITC.

Hemmila teaches several methods of fluoroimmunoassays (FIA) using FITC as a fluorescent label for substrates. The reference teaches that FITC is the probe most widely used in both immunofluorescence and FIA (page 361, column 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute FITC label as taught by Hemmila for the fluorescent labels used by Jeong and Nikiforv or Facemyer and Cremo in the combined references because FITC is a conventionally used fluorescent probe. One would have been motivated to substitute this label in the method of the combined references because the use of FITC was well known in the art as a commercially available label for proteins and offers a safe method for labeling and detecting specific proteins in a sample without the use of hazardous materials such as radioisotopes.

12. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al., Jeong and Nikiforv, and Facemyer and Cremo, in further view of Strachan

and Read (*Human Molecular Genetics*, 1999, BIOS Scientific Publishers Ltd., section 20.2.5).

The claims are drawn to a method of determining the activity of a cell cycle regulatory factor comprising reacting ATP-γS with a substrate for a CDK, labeling the substrate with a labeling enzyme, measuring the amount of label in the product, calculating the activity of the CDK from the measured amount of label in the product with reference to a pre-produced curve (claim 1), and a labeling enzyme peroxidase (claim 5).

Pan et al., Jeong and Nikiforv, and Facemyer and Cremo teach as set forth above. However, the references do not specifically teach labeling the substrate with a labeling enzyme peroxidase.

Strachan and Read teach the conventional use of a peroxidase enzyme as a protein label and detection system and teach that the system offers the use of readily available commercial affinity-purified secondary antibodies (pages 6 and 7 of 9).

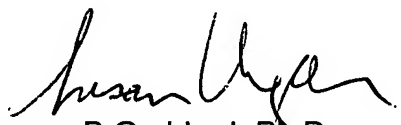
It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the peroxidase label of Strachan and Read for the fluorescent labeling methods of Jeong and Nikiforv and Facemyer and Cremo in the method of the combined references because Strachan and Read teach that peroxidase is a conventional reporter molecule. One would have been motivated to substitute this method as a labeling and detection system for the substrate of the combined references because the method of labeling the substrate with a peroxidase enzyme was well known in the art, conventional, and offers the use of readily

commercial affinity-purified secondary antibodies, which is a safe method of labeling and detection without the use of hazardous materials such as radioisotopes.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Examiner
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